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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,492	02/12/2001	Charles Nicolette	20363-004 (DFCI-4)	7050

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Ivor R. Elrifi, Esq
MINTZ, LEVIN, COHN, FERRIS,
GLOVSKY and POPEO, P.C.
One Financial Center
Boston, MA 02111

EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,492	NICOLETTE ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,35-39,42,45-49,52-55,84,89 and 90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,35-39,42,45-49,52-55,84,89 and 90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/1/03 has been entered.

Claims 32, 35, 36, 42, 45, 46, 52, 53, 54, 84, 89 have been amended. Claims 32, 35-39, 42, 45-49, 52-55, 84, 89, and 90 are pending and under current examination.

Specification

The disclosure is objected to because of the following informalities: figure 13 indicated in the Brief Description of Drawings is missing from the 2/12/01 submission, and figures 11B-13 are missing from the formal drawings submitted 7/19/01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32, 35-39, 42, 45-49, 52-55, 84, 89, and 90 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The amended claims recite "a substantially pure population of educated, antigen-specific cytotoxic immune effetor cells" comprises CD4+ and CD8+ immune effector cells. The phrase "cytotoxic immune effect cells" in claims 32 and 42 is used by the claim to encompass both CD4+ and CD8+ cells, while the accepted meaning is "CD8+ T cells" (See Mesh term database sheet). Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The claims are indefinite because the specification does not clearly redefine the term, "cytotoxic immune effector cells". It is noted that the specification does define "immune effector cells" as to include cytotoxic T lymphocytes and other T cells (Specification, page 9, lines 21-29), but fails to define the term "cytotoxic immune effector cells". It is unclear what cell types the new term includes or excludes, thus, the metes and bounds of the claims are uncertain.

The claims are vague and indefinite because of the term "a *substantially pure* population of educated, antigen-specific cytotoxic immune effector cells expanded in culture". Since said immune effector cells (the starting cell population) appear to

encompass a diverse population of cells such as B cells, monocytes, macrophages, NK cells, and any T lymphocytes (e.g. CD3+, CD4+, or CD8+, defined in the claims and the specification, page 9), it is unclear what cell types are present in the expanded population, and what is considered as "pure". Accordingly, it is unclear the meaning of "substantially pure population" in the context of the claims, thus the metes and bounds of the claims are uncertain.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32, 35-39, 42, 45-49, 52-55, 84, 89, and 90 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

The claims are drawn to a substantially pure population of educated, antigen-specific immune effector cells. Given the broadest reasonable interpretation in light of the specification, said immune effector cells are pharmaceutical composition for treating cancer in animals, particularly humans. With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. "WHEN A COMPOUND OR COMPOSITION CLAIM IS LIMITED BY A PARTICULAR USE, ENABLEMENT OF THAT CLAIM SHOULD BE EVALUATED BASED ON THAT USE". (MPEP 2164.01c) When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. The specification teaches that immunization of mice with the DC-TC hybrid cells induced antigen-specific protection against subsequent tumor cell challenge, and the immunized mice were tumor free (table I). The immunization also protected bone metastasis in these mice (paragraph bridging pages 50-51). The specification though is silent with respect to the effect of the DC-TC hybrids on humans. Applicants submitted a post-filing publication *Parkhurst et al* (J Immunol 2003;170:5317-25) to support the assertion that the instant invention is advantages compared to the cited prior art, because it stimulates both CD4+ and CD8+ T cells, however, the specification only teaches producing CD8+ CTL cells and fails to show that the hybrid cells indeed expanding the population of CD4+ cells (working examples). Moreover, *Parkhurst et al* teach that even though DC-tumor hybrids have been shown to have a protective effect in animal tumor models, in the recent two clinical trials, fusions of DCs and autologous tumors are primarily *ineffective*

for treating tumor in humans. They go on to teach that the electrofused but not the PEG fused hybrid cells may elicit both CD4+ and CD8+ T cell responses (left column, page 5318, particularly lines 7-8 from bottom, and text in page 5322). In view of such, the invention does not appear to be enabled in the absence of clarification of the contradictory evidence found in the references, because the specification uses PEG fusion, and claims encompass any method of fusion and autologous cell fusion.

Given the broadest reasonable interpretation, claims are drawn to contacting "cytotoxic" immune effector cells with DC-tumor hybrid cells and expanding a substantially pure population of cytotoxic immune effect cells, wherein said immune effector cells encompassing B cells, monocytes, macrophages, NK cells, and any T lymphocyte (e.g. CD3+, CD4+, or CD8+) as defined in page 9. In the relevant art, the common knowledge is that the T cell clonal expansion starts with naïve T cells, the art is silent and the specification fails to teach that contacting any one of the above mentioned cell types with said hybrid cells would generate a substantially pure population of CD4+ and CD8+ immune effector cells. According to the common knowledge in the art, B cells, NK cells, and macrophages are terminally differentiated cells, they are unlikely to become CD4+ or CD8+ T cells upon contacting with said hybrid cells. In view of such, the claims do not appear to be enabled in the absence of evidence to the contrary.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 32, 35, 42, 45, and 84 stand rejected, and claims 37, 47, 52, 54, 55, 89, 90 are newly rejected under 35 U.S.C. 102(e) as being anticipated by *Nair et al* (US 6,306,388 or 6,387,701), and as evidenced by *Janeway Jr.* (Immunobiology, 2001), *Hural et al* (J Immunol 2002 ;169 :557-65), and *Powell et al* (J Immunother Emphasis Tumor Immunol. 1995;17:209-21) for reasons of record and following.

In 10/1/03 response, Applicants filed Declaration under 37 CFR § 1.132 to support the assertion that the immune effector cells taught by *Nair et al* do not contain CD4+ cells because Nair introduces RNA into the APCs, therefore endogenous proteins are presented on the cell surface. Thus, the population of immune effector cells educated by contact with the Nair APCs will be CD8+, but not CD4+, because endogenous proteins are presented by Class I MHC molecules.

The Declaration and the argument has been fully considered but they are not persuasive because there is no evidence that the RNA loaded-APCs would only stimulate CD8+ T cells, and because the nature of an immune response is determined by the type of antigens, the state of antigen-presenting cells, and the cell population

contacted with the activated APCs. Note that another patent of *Nair et al* is newly cited to rely upon and as evidence for this rejection.

With respect to the type of tumor antigen in the context of MHC molecule-association, *Janeway Jr.* teaches that tumor antigens could induce both CD8+ and CD4+ T cell responses, "ALTHOUGH IN MOST CASES TUMOR REJECTION ANTIGENS ARE PRESENTED AS PEPTIDES COMPLEXED WITH MHC CLASS I MOLECULES, TYROSINASE HAS BEEN SHOWN TO STIMULATE CD4 T-CELL RESPONSES IN SOME MELANOMA PATIENTS BY BEING INGESTED AND PRESENTED BY CELLS EXPRESSING MHC CLASS II" (14-12, 7th paragraph, Immunobiol), "THE RANGE OF MAGE-TYPE PROTEINS THAT HAS NOW BEEN CHARACTERIZED ENCOMPASSES PEPTIDE EPITOPES PRESENTED BY MANY HLA CLASS I AND II MOLECULES" (14-15, 1st paragraph, Immunobiol). *Hural et al* (J Immunol 2002 ;169 :557-65) teach that naturally processed CD4 T cell epitopes are present in the prostate-specific (tumor) antigen (e.g. the abstract). Clearly, many tumor antigens could associate with MHC class II molecules and induce CD4+ T cell response.

With respect to the antigen-presenting cells, Applicants state in the Declaration that the hybrid cells of the instant application express shared and unique tumor-associated antigens, high levels of MHC class I and II molecules, and adhesion and costimulatory molecules, thus, the population of immune effector cells would contain both CD4+ and CD8+ cells. In response, it is noted that generally speaking, any activated antigen presenting cells would have the recited characteristics. *Janeway Jr.* teaches that activated antigen-presenting cells express both class I and II MHC molecules (fig. 3.19, Immunobiology), and *Powell et al* (J Immunother Emphasis Tumor

Immunol. 1995;17:209-21) teach that tumor antigen did stimulate T cells via accessory molecule by co-stimulatory and adhesion molecules. There is no evidence to the contrary why the APCs taught by *Nair et al* would be an exception. In fact, in the newly cited patent, *Nair et al* clearly teach that the APCs used for loading the tumor RNAs express MHC class II molecules, thus, the subsets of T cells generated contains both CD8+ and CD4+ cells, and they can be distinguished by standard protocols (paragraph bridging columns 3 & 4). Accordingly, the APCs taught by *Nair et al* appear to have the characteristics recited in the Declaration, thus, would stimulate and expand a substantially pure population of immune effector cells as required by the claims.

With respect to the starting material, the immune effector cells before expansion, the specification expanding naïve or educated T cells obtained from peripheral blood (PBMC), which is the same source as taught by *Nair et al*. Moreover, *Janeway Jr.* also teaches that about two thirds of peripheral T cells are CD4+ cells, and about one third are CD8+ cells (Appendix II. CD antigens, Immunobiol). Accordingly, the starting material would already include both cell population in Nair reference, thus, the end product would meet claim limitation.

Claim 52 has been included in this rejection, because in both cited patents *Nair et al* teach that naïve T cells are incubated with RNA loaded APCs (figures 1 & 2 in '388 patent, and column 14, line 13 in '701 patent).

Claims 37, 47, 54, 55, 89, 90 have been included in this rejection, because they further define the hybrid cells used in the process of preparing the immune effector cells, while patentability of a product-by-process claim is determined by the novelty and

nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985).

Accordingly, *Nair et al* anticipate instant claims.

Claims 32, 35, 42, 45, and 84 stand rejected and claims 37, 47, 52-55, 89, 90 are newly rejected under 35 U.S.C. 102(e) as being anticipated by *Granucci et al* (6,156,307), and as evidenced by *Janeway Jr.* (Immunobiology, 2001), *Hural et al* (J Immunol 2002 ;169 :557-65), and *Powell et al* (J Immunother Emphasis Tumor Immunol. 1995;17:209-21).

As an initial matter, it is noted that many of the analysis regarding the nature of the antigen, the starting cell population, and the characteristics of antigen-presenting cells discussed in the *Nair* rejection applies to this rejection.

In 10/1/03 response, applicants filed Declaration under 37 CFR § 1.132 to support the assertion that the immune effector cells taught by *Granucci et al* do not contain both CD4+ & CD8+ cells because *Granucci et al* teach loading antigens that are associated with either Class I or Class II MHC molecules, but not both (referred to column 5 teaching), and the loaded polypeptide antigens are presented by Class II molecules only, thus, the effector cells are not cytotoxic.

The argument has been fully considered but they are not persuasive.

With respect to the types of antigens used in light of the cited patent as a whole, the teaching of *Granucci et al* is not limited to tumor antigen but embraces any antigen which can be associated with either class I molecule such as viruses and bacteria, or

associated with class II molecule such as other bacteria and parasites (fig 5.2, Immunobiol). But since the instant claims are drawn to tumor-DC fusion, tumor antigen is the relevant antigen to discuss. As cited in the immediate preceding rejection, *Janeway Jr.* and *Hural et al* teach that tumor antigens could induce both CD8+ and CD4+ T cell responses.

With respect to antigen-presenting cells, *Janeway Jr.* and *Powell et al* clearly teach that activated APCs express both MHC class I, II, adhesion, and costimulatory molecules. *Granucci et al* clearly teach that the antigen presenting cells used constitutively express B7/BB1 costimulating molecule that would induce naïve T cells to undergo antigen specific clonal expansion (column 10, lines 5-18), and when antigens associated with both class I and II MHC molecules are used, they would trigger the responses of both CD4+ and CD8+ cells.

Moreover, it appears inaccurate to conclude that "the loaded polypeptide antigens are presented by Class II molecules only" because as taught by *Janeway Jr.*, it is the type of antigen loaded that determines its association with MHC molecules, thus, the type of T cells activated (fig 8.31, Immunobiol).

With respect to the starting material, the immune effector cells before expansion, the specification expanding naïve or educated T cells obtained from peripheral blood (PBMC), which is the same source as taught by *Granucci et al.* Moreover, *Janeway Jr.* also teaches that about two thirds of peripheral T cells are CD4+ cells, and about one third are CD8+ cells (Appendix II. CD antigens, Immunobiol). Accordingly, the starting

material would already include both cell population in *Granucci* reference, thus, the end product would meet claim limitation.

Claims 52 and 53 are included in this rejection because *Granucci et al* teach stimulating T cells that are either naïve or antigen-specific (educated) prior to co-culture with the antigen-loaded dendritic cells (column 4, lines 59-61).

Claims 37, 47, 54, 55, 89, 90 have been included in this rejection, because they further define the hybrid cells used in the process of preparing the immune effector cells, while patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985).

Therefore, *Granucci et al* anticipate instant claims.

Response to Arguments

In the Declaration, Applicant repeatedly cited a post-filing publication by *Parkhurst et al* indicating that DC-tumor hybrid cells expressing both MHC class I and class II-restricted tumor-associated epitopes, and thus, are useful for the induction of tumor-reactive CD4+ and CD8+ T cells. While true, there is nothing in *Parkhurst et al* indicate that the APCs used by Nair and Granucci would not express both type of MHC molecules as discussed in detail under 35 USC § 102. In fact, *Parkhurst et al* acknowledges that other antigen presentation system have been developed to stimulate polyclonal immune response against multiple tumor-associated proteins, these systems include the systems of Nair et al (DC-total tumor RNA) and *Granucci et al* (peptide

loaded APCs), and acknowledge that these approaches have induced protective and therapeutic immune responses and are currently being evaluated in human clinical trial (right column, page 5317).

The arguments in Applicants' response and the Declaration focused on the differences in the method of making the immune effector cells, but fail to provide factual evidence showing the structural and functional differences of the instantly claimed product with the product of the prior art. It is noted that the efficiency of various methods of T cell clonal expansion may be different, but the patentability of the instant claims depends on a showing that actual, and unobvious differences exist between the products of the cited prior art and that of the instantly claimed. Applicants are reminded that the patent Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the prior art products do not necessarily or inherently possess characteristics of claimed product, which requires factual evidence demonstrating that actual, unobvious differences exist (or that the claimed products are functionally different than those taught by the prior art) and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPBI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d 1922, 1923 (BPAI 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32, 36, 38, 39, 42, 46, 48, and 49 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Granucci et al* (US 6,156,307) or *Nair et al* (US 6,387,701), and in view of *Altenschmidt et al* (J Immunol 1997;159:5509-15).

The claims are drawn to genetically modified cytotoxic immune effector cells. *Granucci et or Nair et al* teach a substantially pure population of cytotoxic immune effector cells including T cells as discussed in detail in section 102, but they do not particularly teach genetically modifying the immune effector cells.

Altenschmidt et al teach genetically modifying immune effector T cells with a chimeric gene encoding zeta-chain of the TCR and a single chain antibody directed against the human ErbB-2 receptor, which provided the T cells with target tumor cell-specific recognition, and thus obtained anti-tumor activity of modified T cells (e.g. the abstract)

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Nair et al or Granucci et al,* by simply genetically modifying the immune effector T cells with a target cell-specific molecule to enhance the effects of immune effector T cells as taught by *Altenschmidt et al* with a reasonable expectation of success. The ordinary skilled artisan would have

been motivated to modify the claimed invention because the modification would provide enhanced specificity and thus increased antitumor effect. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942 (571-272-0730, after the Office relocation in January, 2004). The examiner can normally be reached on 9:30 am - 6 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QL
December 15, 2003